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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,187	06/12/2002	Michael Hallek	50125/044001	2548

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EXAMINER	
HURT, SHARON L	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 12/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,187	HALLEK ET AL.	
	Examiner	Art Unit	
	Sharon Hurt	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment.. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-43 and 45-64* is/are pending in the application.

4a) Of the above claim(s) ___ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-43 and 45-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/1/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The patent examiner assigned to your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to examiner Sharon Hurt.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27-28, 35-36, 60-61 and 63-64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27, drawn to a method for purifying AAV and/or AAV particles, fails to define the difference between "AAV" and "AAV particles". The two terms are used interchangeable in the specification however no clear definition is provided. Also in claim 27, the term "using" does not constitute an active step.

Claim 28 is drawn to the method in claim 27, wherein the alteration makes an improvement in the purification. The term "improvement" is a relative term failing to particularly point out and distinctly claim the subject matter. One would ask; "improvement compared to what?"

Claims 35 and 62 are drawn to the method in claim 27, wherein amino acids of a functional sequence are inserted into the structural protein. The term "functional sequence" is not defined in the specifications therefore the meaning is unclear.

Claim 36 are drawn to the method in claim 35, wherein the inserted amino acid sequence is...an "antibody epitope". The term "antibody epitope" is unclear and not defined in the specification. Is the "antibody epitope" an epitope that binds to an antibody or an epitope presented by an antibody?

Claims 60-61 and 63-64 are drawn to the methods of 27 and 38, using the structural protein in the form of an AAV particle or AAV capsid. The term "using" does not constitute an active step. The two terms, "AAV particle" or "AAV capsid" are not defined in the specification therefore there is no differentiation in the claims 60 and 36 or in claims 61 and 64.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 31 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claim is drawn to a genus of mutations, those increasing thermal stability of the capsid structural protein(s). The specification provides only a statement that increased thermal stability is desirable, and a suggestion to test a large number of mutants for thermal stability. Thermal stability is not readily predicted,

and the specification provides no guidance on where to alter the primary structure to obtain improved stability of the tertiary and quaternary structure (folded capsid proteins and assembled virus particles). Considering the breadth and unpredictability of the genus, the large number of possible mutations in the capsid structural proteins, and the absence of specific guidance, the specification does not reasonably convey that applicants possessed the mutated structural proteins required by the claim.

Claim 36 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inserting an amino acid sequence into the structural protein of AAV, does not reasonably provide enablement for inserting all of the possible additions listed in the group in claim 36. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use AAV mutations the invention commensurate in scope with these claims. It is well known in the art that virus assembly relies on proper folding of capsid proteins, and large modifications (such as inserting an entire ligand, receptor, antibody, enzyme, protein, growth factor, single chain antibody, etc.) would prevent proper folding. The specifications do not teach, or provide examples, how to insert many of the items from the group in claim 36.

Claims 46 and 47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 46 and 47 are drawn to the methods of 27 and 38, wherein the

mutation(s) and additional mutation(s) are located at the N terminus of the structural protein. Hoque et al., (Biochemical and Biophysical Research Communications 266, 371-376, 1999), teaches the N-terminal region is not accessible in assembled virus because it is located inside the virus-like-particle. Therefore, this method would not work and no examples were provided in the specifications of this application.

Claim Objections

Claim 30 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 30 is drawn to the method of claim 27, wherein the mutated structural protein is capable of particle formation. If the structural protein were not capable of forming particles one would not be able to practice the parent claim 27.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application

filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 27-30, 32-36, 38-43, 45-47 and 60-64 are rejected under 35 U.S.C. 102(e) as being anticipated by Patent 6,491,907.

Claims 27 and dependant claims 28-43 and 45-64 contain on active step of "using". The claim does not specify that the purification method uses chromatography, only that a virus with a mutation is used, and that the mutation alters the chromatographic properties of the virus. Therefore, broad interpretation of the claim reads on any purification method that is performed on a virus, where the virus has a latent ability to be distinguishable from the wild type virus by chromatography.

Claim 27 is drawn to a method for purifying AAV and/or AAV particle with a structural protein of AAV that has at least one mutation on the virus surface that has an alteration in the chromatographic properties. US Patent 6,491,907 (column 25, lines 1-7) teaches AAV capsids that have been modified by insertion of an amino acid sequence(s) into the capsid to confer altered tropisms or other characteristics. The altered sequence would make the AAV capsid purify differently chromatographically, for example on an affinity column. This reference therefore meets every limitation of the claim.

Claim 28 is drawn to the method of claim 27 wherein the alteration in the chromatographic properties makes an improvement in the purification selected from the

group consisting of a concentration of the virus, higher titers, a concentration of the virus particles to higher titers, purification to greater purity, and a more efficient purification. US Patent 6,491,907 (column 13, lines 64-66) teaches a method to purify AAV and AAV particles to produce high-titer stocks.

Claims 29 is drawn to the method in claim 27 wherein the mutation reduces the infectivity of the virus. US Patent 6,491,907 (column 8, lines 51-54, column 21, lines 10-13) teaches the reduction in infectivity.

Claim 30 is drawn to the method in claim 27 wherein the mutated structural protein is capable of particle formation. US Patent 6,491,907 (column 6, lines 6-7, column 14, lines 53-56) teaches the production of AAV particles.

Claim 32 is drawn to the method in claim 27 wherein the structural protein is selected from the group consisting of mutated VP1, VP2, and VP3. US Patent 6,491,907 (column 2, lines 24-28) teaches the mutation by insertion of a sequence into the capsid proteins VP1, VP2, and VP3.

Claim 33 is drawn to the method in claim 27 wherein the mutation in the structural protein is derived from the group consisting of AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, and other AAV serotypes. US Patent 6,491,907 (columns 5-6 lines 66-67 and 1-5) teach the use of parvovirus AAV types 1-6 and other AAV types.

Claim 34 is drawn to the method of claim 27 wherein the mutation in the structural protein is selected from the group consisting of a point mutation, a mutation of one or more amino acid(s), one or more deletion(s), one or more insertion(s), and a combination of said mutations.

Claim 35 is drawn to the method in claim 27 wherein amino acids of a functional sequence are inserted into the structural protein. US Patent 6,491,907 (column 9, lines 48-59, column 15, lines 20-22) teach parvovirus capsid mutations to consist of deletions, insertions, point mutations, and the like.

Claim 36 is drawn to the method in claim 35 wherein the inserted amino acid sequence is selected from the group consisting of a ligand of a receptor, an antibody, an antibody epitope, an antigen, an antigen epitope, a hormone, a hormone receptor, a lectin, a His tag, a nucleic acid binding site, a heparin binding site, an integrin, a cytokine, a growth factor, an epitope, etc. US Patent 6,491,907 (column 6, lines 35-61, column 23, lines 36-59) teach the exogenous targeting sequence may be any amino acid sequence encoding a peptide or protein that alters tropism and includes ligands, receptors, hormones, cytokines, and the like.

Claim 38 is drawn to the method in claim 27 wherein the structural protein comprises at least one other mutation. US Patent 6,491,907 (column 9, lines 41-45) teaches the rAAV genone can encode more than one heterologous nucleic acid sequence (e.g., two, three or more heterologous sequences), generally only limited by the packaging capacity of the virus capsid.

Claim 39 is drawn to the method in claim 38 wherein the other mutation(s) in the structural protein brings about an alteration in the infectivity of the virus. US Patent 6,491,907 (column 8, lines 49-54, 60-66) teaches the hybrid parvovirus may reduce the immune response and rAAV genome is packages with an array of non-homologous capsids to prevent the development of an immune response.

Claim 40 is drawn to the method in claim 38 wherein the other mutation(s) in the structural protein brings about a reduction in antigenicity of the virus. US Patent 6,491,907 (column 5, lines 49-53) teaches the parovirus vectors may possess different or alter characteristics from AAV vectors, including but not limited to antigenic properties, packaging capabilities, and/or cellular tropism.

Claim 41 is drawn to the method in claim 38 wherein the other mutation(s) in the structural protein is selected from the group consisting of one or more deletion(s), on or more insertion(s), and a combination of said modification. US Patent 6,491,907 (column 9, lines 51-59) teaches the parvovirus capsid may include other modifications or mutations (e.g., deletion, insertion, point mutation, and the like).

Claim 42 is drawn to the method in claim 38 wherein the insertion in the structural protein is selected from the group consisting of a cell membrane receptor, ligand, a Rep protein, a Rep peptide, and etc. US Patent 6,491,907 (column 11, lines 51-54) teaches the AAV genome may include AAV Rep proteins.

Claim 43 is drawn to the method in claim 38 wherein the insertion in the structural protein is selected from the group consisting of an integrin, a cytokine, a receptor binding domain of a cytokine, a growth factor, an epitope, etc. US Patent 6,491,907 (column 23, lines 36-45) teaches the insertion of peptides and proteins such as peptide growth factors, cytokines, and the like.

Claim 45 is drawn to the method in claim 38 wherein the additional mutation(s) in the structural protein is/are located on the virus surface. US Patent 6,491,907 (column

23, lines 36-45) teaches the peptides and proteins bind to the cell surface receptors and glycoproteins.

Claims 46 and 47 are drawn to the method in claim 27 and claim 38 wherein the mutation(s), and additional mutation(s), are located at the N terminus of the structural protein. US Patent 6,491,907 (column 2, lines 65-67) teaches the epitope cloned at the N-terminus.

Claims 60 and 61 are drawn to the method in claim 27 and claim 38, using the structural protein in the form of an AAV particle. US Patent 6,491,907 (column 14, lines 61-63, column 19, lines 4-8, 63-66) teach the mutation and additional mutation in the capsid protein can be an AAV particle.

Claim 62 is drawn to the method in claim 35 wherein the amino acids of a functional sequence are suitable for affinity chromatography. US Patent 6,491,907 (column 25, lines 1-7) teaches the amino acid sequence may encode a receptor/ligand or any other peptide or protein that may be used to purify the modified parvovirus by affinity purification, chromatography, etc.

Claims 63 and 64 are drawn to the method in claim 27 and 38 using the structural protein in the form of an AAV capsid. US Patent 6,491,907 (column 7, lines 55-62) teaches a hybrid parvovirus has a parvovirus capsid genome encapsulated within a different parvovirus capsid.

Claim 37 is rejected under 35 U.S.C. 103(a) as being obvious over Patent 6,491,907 in view of Patent 5,276,136.

Claim 37 is rejected under 35 U.S.C. 103(b) as being anticipated by Patent 5,276,136. Claim 37 is drawn to the method in claim 35 wherein a peptide, sequence QAGTFALRGDNPQG, is inserted into the structural protein. US Patent 5,276,136 teaches the following:

Since the A chain was the last chain of laminin for which the entire amino acid sequence was determined, only a few peptides have been described with functional activity. Synthetic peptide PA 21 (residues #1115-1129; cys-gln-ala-gly-thr-phe-ala-leu-arg-gly-asp-asn-pro-gln-gly) (SEQ. ID. NO: 9), which contains the active sequence RGD, induces the attachment of human endothelial cells through an integrin receptor. Since Patent 5,276,136 teaches a ligand for a receptor, it would have been an obvious choice for a ligand to use according to the teachings of Patent 6,491,907.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 48-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patent 6,491,907, in view of Spear et al., (Journal of Virology, Nov. 1977, p.627-634). Claims 48, 50, 52, 54-56 are drawn to the method in claim 27 wherein the mutation in the structural protein is brought about by one or more insertion(s) in or between a specified cleavage site in the VP1-encoding nucleic acid.

Claims 49, 51 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patent 6,491,907, in view of Spear et al., (Journal of Virology, Nov. 1977, p.627-634). Claims 48, 50, 52, 54-56 are drawn to the method in claim 38 wherein the mutation in the structural protein is brought about by one or more insertion(s) in or between a specified cleavage site in the VP1-encoding nucleic acid.

Patent 6,491,907 teachings are described above. The Patent does not teach the specific site to cleave the VP1-encoding nucleic acid or the specific restriction enzyme to use such as *Xhol I*, *Hind II* and *BsrB I* and any combination thereof.

Spear teaches digesting AAV DNA to produce fragments using restriction enzymes Hind II, Hind III and BamH I. It would be obvious to a person of ordinary skill in the art to cleave the AAV DNA with a product that cleaves in the desired region of the genome. A person of ordinary skill in the art would have been motivated to use the appropriate enzyme to cleave the VP1 region as taught by Patent 6,491,907. One would have expected success because Spear uses Hind II to cleave the AAV DNA at a distinct cleavage site for insertion of mutation.

Claims 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patent 6,491,907, in view of Yang et al., (Human Gene Therapy, 9:1929-1937, September 1998). Claims 46-47 are drawn to the method in claim 27 and claim 38 wherein the mutation(s), and additional mutation(s), are located at the N terminus of the structural protein. Patent 6,491,907 teachings are described above. Yang teaches constructiong rAAV vectors encoding modified capsid proteins that allow for cell-type specific targeting. Specifically, a fusion protein was constructed, consisting of the N terminus of the AAV virion protein VP2 and a single chain antibody. This demonstrates that the tropism of the rAAV particle can be altered by addition of chimeric capsid fusion proteins during particle formation. It would have been obvious to a person of ordinary skill in the art to experiment with mutations in the N terminus region as well as the C terminus. A person of ordinary skill in the art would have been motivated to mutate the N terminus region of the structural protein and would have expected success because of the properties of the capsid protein.

Claims 58-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patent 6,491,907 in view of Ruffing et. Al., (Journal of General Virology, 1994, 75, 3385-3392). Claims 58-59 are drawn to the methods in claim 27 and 38 wherein one or more insertion(s) and additional insertion(s) in VP3 are located before or after at least one amino acid in the sequence selected from the group consisting of SEQ ID NO 2-9. Patent 6,491,907 teachings are described above. Ruffing teaches mutation of the VP3 capsid protein alters the infectivity of the virus. Ruffing shows more that one mutation of

the C-terminal region, insertion and deletion, using sequences listed in claims 58-59. It would have been obvious to a person of ordinary skill in the art to insert or delete a short chain of amino acids at different cleavage sites in the capsid protein. A person of ordinary skill in the art would have been motivated to make these deletions because of the known properties of the VP3 region and would have expected success because of the role the capsid proteins play in viral assembly.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon Hurt whose telephone number is 571-272-3334. The examiner can normally be reached on M-F 8:00 - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Housel James can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

December 12, 2005

MARY E. MOSHER, PH.D.
PRIMARY EXAMINER